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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,980	09/24/2004	Ryuji Kaji	TOYA140.001APC	1114

20995 7590 07/14/2006

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/508,980	KAJI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on June 29, 2006 has been received and entered. Claim 8 has been amended. Claims 1-7 have been canceled. Claims 10-16 have been added. No species election is required for new claim 12, because the prior art teaches that each of these serotypes of botulinum toxin may be used to treat muscle hyperactivity (see, e.g., Johnson et al., US 5,939,070, col. 5, lines 31-47). Accordingly, claims 8-16 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 8 recites a purified botulinum neurotoxin that is free from a non-toxic protein of the botulinum toxin. The neurotoxin is the toxin; it is toxic. Thus, this claim is confusing and appears to be a contradiction. Applicants may have meant that the purified neurotoxin from the botulinum toxin complex is free of a non-toxic protein in the complex. Appropriate correction is required.

Claim Rejections - 35 USC § 102

In view of Applicants' amendments to the claims, this rejection is withdrawn.

Claim Rejections - 35 USC § 103

Claims 8 and 9 are again rejected, and claims 12, 13, 15 and 16 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Borodic (US 5,183,462) in view of Johnson et al. (US 5,939,070). This rejection was discussed in the previous Office action.

Applicants assert that Borodic does not disclose a fully purified toxin and that Johnson et al. disclose hybrid botulinum toxins in which the light and heavy chain segments of the neurotoxin are of different serotypes. Applicants assert that Johnson et al. do not disclose using their 150 kD polypeptide neurotoxin to treat muscle hyperactivity, and, therefore, the concept of Johnson et al. is different from that of Applicants. Applicants further assert that no prima facie showing of obviousness can be established by the cited references and that Applicants have shown unexpected results because their 150 kD neurotoxin provides a treatment much more rapidly that the toxins of the prior art.

In reply, the speed or rate at which Applicants' neurotoxins work, relative to other neurotoxins, to treat muscle hyperactivity is not a claim limitation. Claim 9 recites merely that the muscle hyperactivity needs treatment with a fast acting remedy. Applicants have not compared the speed or rate at which their neurotoxins act to other botulinum neurotoxins that are also 150 kD polypeptides, such as those of Johnson et al., i.e., the neurotoxin chain alone, not complexed to the hemagglutinin moiety or other non-toxic proteins in the progenitor complex. The claims recite a method of treatment using a purified botulinum toxin from which a non-toxic protein has been removed, which reads on using any 150 kD botulinum neurotoxin peptide. Whether the light and heavy chain portions are from the same or different serotypes is not a claim limitation. As previously, discussed, Borodic discloses a method of treating various systemic types of dystonia and muscle hyperactivity with a fast-acting remedy, comprising administering a partially purified botulinum toxin to a patient with muscle hyperactivity (see col.

1, lines 6-43, and col. 4, lines 18-29). The preferred botulinum toxin is Type A, which is commercially available as a pharmaceutical preparation of known concentration (OCULINUM), although other pharmaceutical grade preparations may be used (see col. 4, line 52, to col. 5, line 30).

Johnson et al. disclose purified preparations of *C. botulinum* toxins that may be used to treat involuntary muscle disorders (see col. 5, lines 47-59; and col. 6, lines 10-67). Some of the non-toxic binding proteins have hemagglutinating ability (see col. 5, lines 47-50) and are antigenic (see col. 5, lines 54-67). It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use a purified botulinum toxin composition, such as one of those of Johnson et al. (just the neurotoxin polypeptide), e.g., purified Type A or Type B toxin (see col. 7, line 55, to col. 8, line 60; and col. 6, lines 37-59), in the method of Borodic, because Johnson et al. teach that, with a purified preparation, the active protein can exert its therapeutic effect without generating hemagglutination or an immune response in the patient (see col. 6, lines 1-10) and that a lower protein load may be administered to the patient to achieve the same effect (lower chance of an allergic reaction or other side effects). Additionally, the active neurotoxin polypeptide may be produced by expressing only one gene in a host cell and culturing the host cell, as all of the botulinum neurotoxin genes are known (see col. 11, lines 33-45). Thus, purification from the natural source, which is hazardous, is not required, unwanted protein sequences that may lead to non-specific effects are removed, and large-scale production in a suitable expression system is possible (see col. 12, lines 4-31). The neurotoxin polypeptide is biologically active, but not hazardous (see col. 2, lines 25-42, and col. 12, lines 23-31).

In view of the foregoing, the rejection of record is maintained.

Claims 8-9 are again rejected, and claims 12-16 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Donovan (US 2001/0053369) in view of Johnson et al. (US 5,939,070). This rejection was discussed in the previous Office action.

Applicants assert that their invention is not obvious, because Donovan does not disclose a 150 kD neurotoxin for treating muscle hyperactivity. Also, the advantage that treatment with a fast-acting remedy is exhibited faster than the progenitor toxin is not expected from the combination of these references.

In reply, Applicants' remarks are somewhat unclear and confusing. Applicants may have meant that the 150 kD neurotoxin works faster than the progenitor toxin, which is an advantage, and that this advantage would not have been expected from the teachings of the cited references. As discussed above, the relative rate at which Applicants' neurotoxins work, compared to other neurotoxins, is not a claim limitation. As discussed previously, Donovan does not disclose a 150 kD neurotoxin in purified form that is administered to treat muscle hyperactivity, but Johnson et al. do. Johnson et al. also disclose advantages of preparing the neurotoxin polypeptide as a therapeutic compound without the other polypeptides in the botulinum complex, as noted above. The purified neurotoxin is not immunogenic, which leads to drug resistance. It causes fewer side-effects because fewer polypeptides are present, and it is easy to produce on a large-scale safely, because only one known gene need be cloned into a suitable host cell, followed by culturing of the host cell. Isolation from a toxic natural source is not required (see col. 11, lines 33-45; col. 12, lines 4-31; and col. 2, lines 25-42).

Regarding claim 14, Donovan discloses that the amount of botulinum neurotoxin used can be varied and that the amount needed depends on the disorder to be treated, the severity of the disorder, the weight and health of the patient, etc. Methods for determining the appropriate dose are routine in the art and are determined on a case-by-case basis by the physician (see

paragraph 110). Thus, it would have been obvious to one of ordinary skill in the art of medicine at the time that the invention was made to adjust the dose administered to an effective dose after administration of the neurotoxin drug had begun, because Donovan discloses that such an adjustment is routine to physicians. It would have been obvious to a physician that if the dose administered was not effective, a higher dose should be given, and that if the dose administered produced intolerable side-effects, a lower but still effective dose should be given.

In view of the foregoing, the rejection of record is maintained.

Claims 8-9 are again rejected, and claims 10-16 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. (US 6,319,505) in view of Johnson et al. (US 5,939,070) and Allergan, Inc. (package insert for Botox®, http://www.botox.com/download/ BotoxPI.pdf, printed on December 13, 2005). This rejection was discussed in the previous Office action.

Similarly to the foregoing rejection, Applicants assert that their invention is not obvious because Aoki et al. do not disclose a 150 kD neurotoxin, and the combination of the cited references does not disclose that treatment with a 150 kD neurotoxin is faster than treatment with the progenitor botulinum toxin.

In reply, similarly to the foregoing rejections, the relative rate at which Applicants' neurotoxins work, compared to other neurotoxins, is not a claim limitation. As discussed previously, Aoki et al. do not disclose a 150 kD neurotoxin in purified form that is administered to treat muscle hyperactivity, but Johnson et al. do. Johnson et al. also disclose advantages of preparing the neurotoxin polypeptide as a therapeutic compound without the other polypeptides in the botulinum complex, as noted above. The purified neurotoxin is not immunogenic, which leads to drug resistance. It causes fewer side-effects because fewer polypeptides are present, and it is easy to produce on a large-scale safely, because only one known gene need be cloned

into a suitable host cell, followed by culturing of the host cell. Isolation from a toxic natural source is not required (see col. 11, lines 33-45; col. 12, lines 4-31; and col. 2, lines 25-42).

Regarding claims 10 and 11, Aoki et al. disclose that human serum albumin may be added to a preparation of a botulinum neurotoxin to stabilize it (see col. 4, lines 8-9).

Regarding claim 14, Aoki et al. disclose that the dose and dosing schedule of botulinum neurotoxin are at the discretion of the physician and are determined by the neurotoxin's effect and by the safety to the patient (see col. 4, line 59, to col. 5, line 3). Thus, it would have been obvious to one of ordinary skill in the art of medicine at the time that the invention was made to adjust the dose administered to an effective dose after administration of the neurotoxin drug had begun, because Aoki et al. disclose that such an adjustment is routine to physicians. It would have been obvious to a physician that if the dose administered was not effective, a higher dose should be given, and that if the dose administered produced intolerable side-effects, a lower but still effective dose should be given.

In view of the foregoing, the rejection of record is maintained.

Claims 8-9 are again rejected, and claims 12, 13, 15 and 16 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Graham (US 6,395,277) in view of Johnson et al. (US 5,939,070), Allergan, Inc. (package insert for Botox®, http://www.botox.com/download/BotoxPI.pdf, printed on December 13, 2005) and Shore Laser ("Botulinum toxin for the treatment of facial lines and wrinkles," http://www.shorelaser.com/BottoxA.html, printed on December 13, 2005). This rejection was discussed in the previous Office action.

Applicants' response to this rejection is similar to those against the three rejections above. Applicants assert that their invention is not obvious because Graham does not disclose

a 150 kD neurotoxin, and the combination of the cited references does not disclose that treatment with a 150 kD neurotoxin is faster than treatment with the progenitor botulinum toxin.

The same reply to Applicants' response, therefore, is pertinent here as well. The relative rate at which Applicants' neurotoxins work, compared to other neurotoxins, is not a claim limitation. As discussed previously, Graham does not disclose a 150 kD neurotoxin in purified form that is administered to treat muscle hyperactivity, but Johnson et al. do. Johnson et al. also disclose advantages of preparing the neurotoxin polypeptide as a therapeutic compound without the other polypeptides in the botulinum complex, as noted above. The purified neurotoxin is not immunogenic, which leads to drug resistance. It causes fewer side-effects because fewer polypeptides are present, and it is easy to produce on a large-scale safely, because only one known gene need be cloned into a suitable host cell, followed by culturing of the host cell. Isolation from a toxic natural source is not required (see col. 11, lines 33-45; col. 12, lines 4-31; and col. 2, lines 25-42).

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1653

rk/2006-07-10

Rosanne Kosson

ROBERT A. WAX
PRIMARY EXAMINER